REVIEW ARTICLE

SGLT2i as a First-line Antihyperglycemic in the Management of Type 2 Diabetes in the Context of Indians: A Systematic Review and Consensus

Awadhesh Kumar Singh[1*], Anoop Misra[2], Ashok Kumar Das[3], Anish Behl[4], Ankit Srivastava[5], Arunachalam Paneerselvam[6], Balaji Chidambaram[7], Banshi Saboo[8], Bipin Sethi[9], Brij Mohan Makkar[10], Ganapathi Bantwal[11], Hemant Thacker[12], Jayant Panda[13], Jothydev Kesavadev[14], Krishna G Seshadri[15], Mangesh Tiwaskar[16], Minakshisundaram Shunmugavelu[17], Rakesh Sahay[18], Sambit Das[19], Sanjay Agarwal[20], Shehla Shaikh[21], Surendra Kumar Sharma[22], Sunil Gupta[23], Supratik Bhattacharyya[24], Viswanathan Mohan[25], Vijaya Kumar Gunupati[26]

Received: 05 October 2023; *Accepted:* 10 October 2023

Abstract

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been used for almost a decade and have proven to be effective not only in managing Type 2 diabetes (T2D), but their cardio and renal protective features make them very useful in managing patients with risk of multiple comorbidities. This systematic review was undertaken by the authors because there is no evidence currently available in India that has studied the suitability of SGLT2i as a first-line agent in patients newly diagnosed with T2D in India.

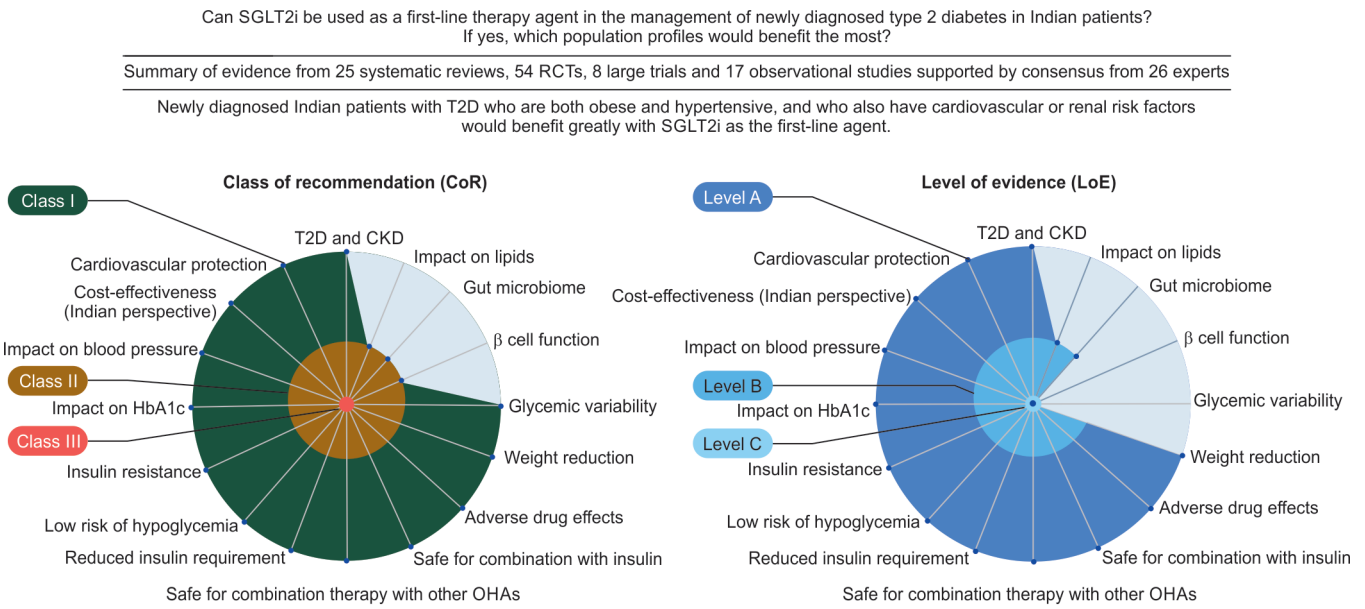
Materials and methods: First, literature was searched to identify features that are considered important when deciding on a first-line agent for managing T2D. A total of 5 broad topics were identified-glycemic control, extra glycemic effects, antihyperglycemic combination therapy, safety, and cost-effectiveness. These domains had further subheadings, and a total of 16 domains were identified. Metformin is the drug of choice as a first-line agent in such situations and has been considered the gold standard for evaluating the effects of SGLT2i across these domains. A systematic literature review on each domain was conducted to compare SGLT2i with the gold standard in Indian patients newly diagnosed with T2D. Evidence was graded (levels of evidence (LoE)—A, B, and C), and recommendations (class of recommendation (CoR)—I, II, and III) were classified by the expert group as defined in the methodology.

Results: According to the systematic reviews conducted, 11 domains had Level A evidence, 2 domains (impact on lipids and gut microbiome) had Level B, and 3 domains had Level C (β-cell function, renal protection, and glycemic variability) evidence. Based on evidence and expert opinion, the authors recommend SGLT2i as a first-line agent for managing newly diagnosed patients with T2D with a Class I recommendation for 13 domains and Class II for the remaining 3 (impact on lipids, gut microbiome, and β-cell function). Although a poorer level of evidence (Level C) was available for the glycemic variability domain, the authors still reported this as Class I recommendations according to their expert opinion and consensus.

Conclusion: This article advocates adopting SGLT2 inhibitors as the primary treatment choice for treating patients with newly diagnosed T2D in India.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0422

Visual Abstract



Source: SGLT2i as a first-line anti-hyperglycemic in the management of type 2 diabetes in the context of Indians: A systematic review and consensus, Singh et al. 2023

[1]Consultant Endocrinologist, Department of Diabetology, GD Hospital & Diabetes Institute, Kolkata, West Bengal; [2]Consultant Endocrinologist, Department of Diabetes and Endocrinology, Fortis-C-DOC Hospital, Delhi; [3]Consultant Endocrinologist, Department of Endocrinology, Pondicherry Institute of Medical Sciences, Pondicherry; [4]Consultant Endocrinologist, Department of Endocrinology, Wellness Superspeciality Centre & Apollo BGS Hospitals, Mysuru, Karnataka; [5]Consultant Endocrinologist, Department of Endocrinology, Arogya Diabetes & Endocrine Centre, Ranchi, Jharkhand; [6]Consultant Diabetologist, Department of Diabetology, Aruna Diabetes Centre, Chennai; [7]Consultant Diabetologist, Department of Diabetology, Nithyashree Balaji Diabetes Centre, Kumbakonam, Tamil Nadu; [8]Chief Diabetologist, Department of Diabetology, Dia Care Hormone Clinic, Ahmedabad, Gujarat; [9]Consultant Endocrinologist, Department of Endocrinology, Care Hospitals, Hyderabad, Telangana; [10]Senior Diabetologist and Obesity Specialist, Department of Diabetology, Dr Makkar's Diabetes and Obesity Centre, Delhi; [11]Consultant Endocrinologist, Department of Endocrinology, St Johns Medical College, Bengaluru, Karnataka; [12]Consultant Physician, Cardio-Metabolic Specialist, Department of Internal Medicine, Bhatia Hospital (Tardeo), Breach Candy Hospital (Breach Candy), Mumbai, Maharashtra; [13]Professor and Head, Department of Internal Medicine, SCB Medical College & Hospital, Cuttack, Odisha; [14]Consultant Diabetologist, Department of Diabetology, Jothydev's Diabetes & Research Center, Trivandrum, Kerala; [15]Senior Consultant, American Board-Certified Endocrinology, Department of Diabetes and Metabolism, Diabetes and Endocrinology Clinic, Chennai, Tamil Nadu; [16]Consultant Diabetologist, Department of Diabetology, Shilpa Medical Research Centre, Mumbai, Maharashtra; [17]Consultant Endocrinologist, Department of Endocrinology, Trichy Diabetes Speciality Centre, Tiruchirappalli, Tamil Nadu; [18]Professor and HOD, Department of Endocrinology, Osmania Medical College, Hyderabad, Telengana; [19]Consultant Endocrinologist, Department of Endocrinology, HiTech Medical College and Hospitals, Bhubaneswar, Odisha; [20]Consultant Endocrinologist, Department of Diabetes Care, Aegle Clinic; Department of Medicine and Diabetes, Ruby Hall Clinic, Pune; [21]Consultant Endocrinologist, Department of Endocrinology, Saifee Hospital, Mumbai, Maharashtra; [22]Consultant Endocrinologist, Department of Endocrinology, Diabetes Thyroid and Endocrine Centre, Jaipur, Rajasthan; [23]Consultant Diabetologist, Department of Diabetology, Sunil's Diabetes Care & Research Centre, Nagpur, Maharashtra; [24]Consultant Endocrinologist, Department of Endocrinology, Apollo Clinic, Kolkata, West Bengal; [25]Chairman and Chief of Diabetology, Department of Diabetology, Dr Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu; [26]Consultant Diabetologist, Department of Diabetology, Diabetes Medicare Centre, Chennai, Tamil Nadu, India; *Corresponding Author

How to cite this article: Singh AK, Misra A, Das AK, *et al.* SGLT2i as a First-line Antihyperglycemic in the Management of Type 2 Diabetes in the Context of Indians: A Systematic Review and Consensus. J Assoc Physicians India 2023;71(12):62–74.

Introduction

Type 2 diabetes (T2D) as a disease presents the ultimate challenge for researchers, clinicians, and patients in the 21st century. Being a disorder that arises from a complex interplay between genetics, environmental, and lifestyle factors, affecting other homeostatic functions of the body synchronized by insulin activity, strategizing the aims of antidiabetic therapy itself can become an arduous task for the clinical community, let alone the therapy. It can be argued agreeably that the Indian population is already at significant risk for developing T2D, but these risk factors are not unique to T2D; instead, they contribute to a battery of other disorders that creep silently and become salient drivers of all-cause mortality in people with T2D.[1]

The high prevalence of coronary and peripheral artery disease in people with T2D has been well recognized for more than a century, yet objectives focusing on glycemic control, insulin resistance, and lifestyle interventions, which are central to the management of T2D, remain elusive in terms of their direct impact on the improvement of cardiovascular (CV) event rates.[2] The last decade has seen several clinical trials of antihyperglycemic agents (AHAs) reporting promising results for CV and renal outcomes. Not only has this led to debates on the ideal drug choice for first-line treatment in T2D in general, but it has also led to the identification of patient profiles that may benefit more from cardiac to renal protective first-line antihyperglycemic treatments—the younger Indian adults with T2D.[3]

The primary objective of this paper is to ascertain whether sodium-glucose cotransporter-2 inhibitors (SGLT2i) can be utilized as a first-line agent in patients newly diagnosed with T2D. Metformin is the gold standard in managing such patients, and thus, a direct structured, evidence-based comparison with SGLT2i is imperative for elucidating whether SGLT2i can actually be prescribed in this profile of Indian patients.

Materials and Methods

A lot has changed in managing T2D, both from a metabolic and a pharmacotherapeutic perspective. Thus, the expectations from a first-line therapy agent have also evolved. An exhaustive literature search was done to identify the most relevant factors determining an agent's suitability as a first-line therapy, in general, and in T2D. Supplementary material 1 (SM1) delineates the search strategy and methods.

Table 1 highlights a list of the topics and their respective domains that were identified as considerations before starting a patient with T2D on first-line monotherapy. Systematic literature search results and a Delphi-based discussion of the expert panel influenced this list of these factors.

A systematic literature search was conducted for each factor identified in Table 1. Cochrane, PubMed, Google Scholar, Science Direct, Clinical Trials (.gov), Clinical Trials Registry of India, medRxiv, Prospero, and Gray literature databases were searched with respective search strategies. The search criteria, strategies, methods, and selected papers are tabulated in Supplementary material 1 (SM1). For all databases, the following population (P), intervention (I), comparison (C), and outcomes (O) were used (mentioned in Supplementary material 2 (SM2).

The context-based search strategy was as follows:

- P = P1 OR P2 OR P3, P1: newly diagnosed people with T2D, P2: people with T2D who were only on diet and lifestyle interventions without any drug therapy, P3: people with T2D who may have been a previous therapy for T2D but were included in the study after a washout period of at least 4 weeks.
- I = I1 OR I2 OR I3 OR I4, I1: dapagliflozin monotherapy, I2: Canagliflozin monotherapy, I3: empagliflozin monotherapy, I4: ertugliflozin monotherapy, I5: remogliflozin monotherapy.
- C = C1 OR C2. C1: placebo, C2: metformin.
- O = based on the factors.

Appropriate search strategies were created for different databases, and relevant papers were selected as per the selection criteria. Evidence was synthesized for all domains, and the findings were presented to the expert panel.

Class of recommendation (CoR) indicates how strong a recommendation is, considering the assumed benefit vs risks and costs on a scale from I to III. Recommendation classes I and III each convey a clear message, namely a general consensus that a measure is either useful (CoR I), not useful, or even harmful (CoR III). If there is no general consensus or only doubtful evidence, an optional recommendation is conveyed with CoR II. The level of evidence (LoE) indicates how reliable the evidence underlying each recommendation is on a scale from A to C. Importantly, the CoR and LoE are independent of each other; for example, strong recommendations may build on weak evidence if the assumed benefit of an intervention or a diagnostic procedure greatly outweighs the potential risks (Table 2).

The authors framed recommendations after carefully reviewing the literature and expert consensus. Finally, all recommendations were classified into different classes. This methodology has been used elsewhere as well.[4]

Results

Glycemic Control

Glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) values are typically used to assess glycemic control. Control of postlunch glucose levels will help in maintaining the HBA1c levels. PPG and glycemic variations are risk factors for complications related to T2D. SGLT2i effectively reduces HbA1c levels, a measure of long-term blood sugar control, along with FPG and PPG.

Impact on HbA1c

Seven studies were included in which SGLT2i was directly compared with metformin. Of these seven studies, six randomized controlled trials (RCTs) and one systematic review and meta-analysis were included.

An RCT conducted by List et al.[5] in 2009 reported that adjusted mean reductions of HbA1c of dapagliflozin 10 and 50 mg (−0.85 to −0.90%) were slightly better than metformin (−0.73%). Adjusted mean PPG area under the curve (AUC) reductions in the dapagliflozin group (−7,053 to −10,149 mg/minute/dL) were superior when compared to metformin (−5,891 mg/minute/dL). In 2013, Ferrannini et al.[6] reported that both empagliflozin (−0.51–0.60%) and metformin (−0.64%) significantly reduced HbA1c levels during a 90-week trial. Ipragliflozin showed a better decrease in HbA1c (−0.49 to −0.81%) compared to metformin (−0.72%) and placebo, based on a study by Fonseca et al.[7] in 2013. RCT conducted by Aronson et al.[8] in 2018 reported that ertugliflozin at a 26-week period showed better mean HbA1c values (7.3%) when compared to placebo/metformin (7.8%). Shibuya et al.[9] in 2018 reported that Luseogliflozin (7.8 vs 6.5) had shown a better reduction in HbA1c when compared to metformin (7.4 vs 7.3). Hao et al.,[10] in 2022, reported that HbA1c was significantly lower in the canagliflozin group (−0.8 ± 0.4) compared to the metformin group (−0.2 ± 0.2). A systematic review and meta-analysis conducted by Pinto et al.[11] (39 RCTs, *n* = 25,468) in 2015 reported that SGLT2i was similar to metformin in decreasing HbA1c but was superior to placebo.

Recommendations and statements	*CoR*	*LoE*
SGLT2i can be considered a first-line in the management of T2D than metformin based on its impact on HbA1c	I	A

Glycemic Variability (GV)

Glycemic variability (GV), or glycemic fluctuation, is a clinical predictor and a key objective in managing diabetes to prevent

Table 1: List of topics and their respective domains

Glycemic control	*Extraglycemic effect*	*Antihyperglycemic combination therapy*	*Safety*	*Cost-effectiveness*
Direct impact on HbA1c	Preserve and enhance β-cell function	Safe for combination therapy with any OHAs	Low risk of hypoglycemia	Cost-effectiveness
Reduce GV	Improvement in insulin resistance	Safe for combination with insulin and reduces insulin requirement	Adverse drug effects	
	Impact gut microbiome			
	Weight reduction			
	BP regulation			
	Lipid-lowering effect			
	Renal protection			
	CV protection			

Table 2: Class of recommendation (CoR) and LoE

CoR		*LoE*		
	Definition		*Definition*	*Interpretation*
I	Evidence or general agreement that a treatment/test/procedure is beneficial, useful, or effective and that potential benefits clearly outweigh the potential risk	A	RCT or meta-analysis of RCTs with CVD outcomes; single trial enough if sufficient power and without important limitations	Strong evidence. Evidence of high certainty. It is unlikely that future studies will change the effect estimate substantially
II	Conflicting evidence or opinion about the benefit, usefulness, and effectiveness of a treatment/test/procedure or uncertainty about the benefit–risk balance	B	RCT with surrogate measures; observational studies with CVD outcomes and no major limitations; meta-analyses including the above study types	Moderate evidence. Evidence with some future studies may modify, at least the magnitude of, the effect estimate
III	Evidence or general agreement that a treatment/test/procedure is not beneficial, useful, or effective or that potential risks outweigh the potential benefit	C	Observational studies of surrogate measures; any study type may be downgraded to level C due to limitations; expert opinion	Weak evidence. Evidence of low certainty. Future studies may change the effect estimate substantially

vascular complications and enhance glycemic control.[12] Indexes representing GV include the mean amplitude of glucose excursion (MAGE), mean blood glucose (MBG) levels, standard deviation of mean blood glucose (SDMBG), and percentage of time maintaining euglycemia.[12,13]

Due to the nonavailability of literature that directly compares SGLT2i with metformin, we have included two RCTs, which compared SGLT2i with placebo in drug-naive patients or with a drug washout period. There was no literature that compared the effect of metformin monotherapy on GV. Many studies compared metformin in prediabetics or in conjunction with another oral antihyperglycemic medication or insulin. We included one study comparing metformin with post-meal exercise regarding GV.

Nishimura et al.[14] in 2015 conducted an RCT and reported that patients treated with empagliflozin showed no significant changes in MAGE, but curves of mean glucose [continuous glucose monitoring (CGM)] lowered in the empagliflozin group when compared to the placebo. It helped in improving daily glucose control. An RCT conducted by Li et al.[15] in 2016 reported that post-24 weeks, there was a significant improvement in MAGE (3.48 ± 0.98 vs placebo group 5.37 ± 2.16, $p = 0.010$) and SDMBG (2.43 ± 1.09 vs 1.51 ± 0.42, $p < 0.05$) with dapagliflozin therapy. Patients exhibited a reduction in 24-hour MBG (7.50 ± 1.49 vs 9.46 ± 1.16 mmol/L, $p = 0.026$) with lower mean plasma glucose concentrations.

In 2017, Erickson et al.[16] conducted a randomized crossover design study that revealed noteworthy findings (metformin vs postmeal exercise). The study demonstrated that metformin reduced time-averaged glucose levels (24-hour main effect: $p = 0.040$, 12-hour main effect: $p = 0.033$). Additionally, exercise was associated with a decrease in MAGE (24-hour main effect: $p < 0.001$, 12-hour main effect: $p = 0.042$) as well as metformin (12-hour main effect: $p = 0.028$). Furthermore, both exercise (24-hour main effect: $p = 0.043$, 12-hour main effect: $p < 0.001$) and metformin treatment (12-hour main effect: $p = 0.070$) contributed to a reduction in standard deviation.

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may be as effective as metformin in terms of impact on GV	I	C

Extraglycemic Effect

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) improves β-cell function and insulin sensitivity and reduces insulin resistance without affecting insulin secretion. They preserve β-cell mass, improve its function, and help in better long-term glycemic control. SGLT2i has been discovered to change the makeup of gut bacteria, potentially boosting the growth of beneficial bacteria and enhancing gut health.

β-Cell Function

The fundamental pathogenic consequences of T2D include progressive β-cell dysfunction and failure. Diminished β-cell function on diagnosis and sustained decline in β-cell mass and function in T2D suggests that medical management targeting pathogenic β-cell deterioration is needed.[17] The proinsulin/insulin ratio (PI/IR)[18] *via* β-cell dysfunction and the homeostasis model assessment of β-cells (HOMA-β)[19] can be measured in diabetes. While the decrease in PI/IR generated by proinsulin shows improvement in the secretory β-cells, the increase in HOMA-β shows retention of β-cell function.[20]

Due to the nonavailability of literature directly comparing SGLT2i with metformin, we have included six studies that compared SGLT2i with a placebo. Of these six studies, four were RCTs, and two were observational studies. There was no literature that compared the effect of metformin monotherapy on β cell function. Many studies compared the use of metformin in rats or in conjunction with another oral antidiabetic medication or insulin. We have included two important studies done on metformin regarding β-cell function.

Randomized controlled trials (RCT) conducted by Inagaki et al.[21] in 2013 proved that canagliflozin improved β-cell function (HOMA-β) (2.97 ± 1.84–6.98 ± 1.94) and PI/IR (−0.0482 ± 0.0177 to −0.0500 ± 0.0186) compared to placebo. Another study by Kutoh et al.[22] in December 2018 suggested that SGLT2i preserved and enhanced β-cell function and reduced insulin sensitivity. β-cell function improvement was observed in studies conducted by Stenlöf et al.[23] in 2013 and Kutoh et al.[24] in March 2018, which reported an increase in HOMA-β and a decrease in PI/IR observed when patients were on canagliflozin (100 and 300 mg) compared with a placebo. Ferrannini et al.[25] in 2022 reported that SGLT2i-induced glucosuria improved β-cell function and insulin sensitivity compared to placebo. A study conducted by Polidori et al.[26] in 2014 [canagliflozin treatment and trial analysis–monotherapy (CANTATA-M)] revealed that SGLT2i improved insulin secretion by the β cells of the pancreas.

Within the context of the United Kingdom Prospective Diabetes Study (UKPDS),[27] individuals diagnosed with newly onset T2D and treated with metformin experienced an initial boost in β-cell function (evaluated through HOMA) during the 1st year. Nevertheless, this improvement was subsequently followed by a decline despite the persistent enhancement of insulin sensitivity due to metformin. Similarly, findings from the A Diabetes Outcome Progression Trial (ADOPT)[28] study, which concentrated on individuals recently diagnosed with T2D, indicated a minor initial advantage of metformin in terms of β-cell function [measured in response to oral glucose tolerance test (OGTT)], which was subsequently accompanied by a gradual decrease. Many studies have also shown that metformin neither preserves β-cell function[29] nor prevents progressive β-cell failure.[30,31]

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be as effective as metformin in terms of impact on β cell function	II	C

Insulin Resistance

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) enhances β-cell activity by reducing glucotoxicity rather than promoting insulin release. They also reduce insulin resistance and boost insulin sensitivity.[32] Homeostatic model assessment of insulin resistance by homeostasis model assessment-estimated insulin resistance (HOMA-IR) index mainly reflects liver insulin resistance, the glucose clamp method mainly reflects muscle insulin resistance, and the insulin sensitivity index reflects insulin sensitivity in both liver and muscle.[33]

A total of two studies were included in which SGLT2i was directly compared with metformin. Of these two studies, one RCT and one systematic review and meta-analysis were included.

Hao et al.,[10] in 2022, conducted an RCT that compared canagliflozin to metformin with regard to insulin resistance (HOMA), subcutaneous, and visceral adipose tissue. It was noted that patients on canagliflozin (2.5 ± 0.4 vs 1.7 ± 0.5) had a better reduction in HOMA-IR and visceral adipose tissue compared to metformin (2.4 ± 0.4 vs 2.1 ± 0.4). A systematic review and meta-analysis conducted by Fakhrolmobasheri et al.[34] (16 RCTs, $n = 1,177$) reported that SGLT2i significantly increased insulin sensitivity [standardized mean difference (SMD) 0.72 (0.32–1.12)] in T2D patients and are not inferior to metformin in reducing insulin resistance.

Recommendations and statements	CoR	LoE
SGLT2i as a first-line agent may be as effective as metformin in terms of impact on insulin sensitivity	I	A

Gut Microbiome

The gut microbiota converts nondigestible carbohydrates into short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, which are then used to control host metabolism. Therefore, changes in the microbiota (gut dysbiosis) can lead to disorders in other organs as well, such as the brain, heart, pancreas, liver, adipose tissues, muscles, and kidneys, in addition to the digestive system.[35] Certain bacterial populations (*Roseburia*, *Eubacterium*, *Escherichia–Shigella*, *Bilophila*, and *Hungatella*) that are generally found in the intestines (gut microbiota), are being considered crucial in the development of obesity, metabolic syndrome, and T2D when certain conditions cause gut dysbiosis. Alterations in the microbiota can result from exposure to various environmental factors, including diet, toxins, drugs, and pathogens.

As per inclusion criteria, only one RCT was included that compared SGLT2i with metformin in drug-naive patients.

An RCT conducted by Deng et al.[36] in 2022 reported that empagliflozin significantly reshaped the gut microbiota and increased the levels of plasma metabolites such as sphingomyelin, short-chain fatty acid-producing bacteria (*Roseburia* and *Eubacterium*) and reduced harmful bacteria (*Escherichia–Shigella*, *Bilophila*, and *Hungatella*). While metformin treatment was only associated with changes in blood glucose levels and body weight-related modifications in plasma metabolites and gut bacteria, empagliflozin modified plasma metabolites and gut bacteria related to blood glucose levels, inflammatory factors, and cardiovascular disease (CVD)—related factors.

According to current research and knowledge, metformin significantly affects the gut microbiota and microbial metabolites, while SGLT2i have slighter effects. Many human studies[37–40] have shown that metformin strongly altered the gut microbiome and its function in individuals with treatment-naive T2D.[39] There is a paucity of SGLT2i studies on humans, and animal studies have shown limited benefits on gut microbiota. Additionally, the positive influence of SGLT2i could be attributed to the possibility that participants were previously under metformin treatment, masking the potential influence of SGLT2i on the gut microbiome.[41]

Recommendations and statements	CoR	LoE
SGLT2i as a first-line agent may be as effective as metformin in terms of impact on the gut microbiome	II	B

Impact on Weight

Type 2 diabetes (T2D) is associated with obesity and physical inactivity. The lack of weight management in T2D patients and the urgent need to identify effective ways to address diabetes and obesity have given rise to a new term: diabesity.[42] A biphasic weight loss pattern has been observed in clinical studies with SGLT2i: a substantial early impact, perhaps due to improved fluid excretion, was followed by a steady rise, with mean weights lower than baseline at any assessment.[43,44] The initial weight loss is due to caloric loss owing to glucose excretion (calorie restriction mimicry) and water loss due to osmotic diuresis.[45]

Seven studies were included in which SGLT2i was directly compared with metformin. Of these seven studies, one systematic review and meta-analysis, six RCTs were included.

An RCT conducted by List et al.[5] in 2009 reported a greater reduction in body weight by different doses of dapagliflozin (–2.5 to –3.4) compared to metformin (–1.7). In 2013, Ferrannini et al.[6] reported that empagliflozin (–1.87 to –2.08) showed a better reduction in body weight when compared to metformin (–0.89) during a 90-week trial. In a study conducted by Fonseca et al.[7] in 2013, dose-dependent weight loss was higher in the ipragliflozin group (–0.50 to –1.67) when compared to metformin (–0.12). The mean change from baseline to 52 weeks in empagliflozin and metformin groups was –3.6 and –3.7, respectively, as Aronson et al.[8] reported in 2018. An RCT conducted by Shibuya et al.[9] in 2018 has shown that luseogliflozin (27.9 vs 27 kg/m^2) was superior to metformin (27.2 vs 27.3 kg/m^2) in reducing body mass index (BMI). Hao et al.[10] in 2022 reported a reduction in BMI (–0.5 vs –0.2), waist–hip ratio (–0.03 vs –0.01), subcutaneous adipose tissue (–3.5 vs –2.4) from baseline to 12 weeks in canagliflozin group when compared to metformin. Systematic review and meta-analysis conducted by Pinto et al.[11] in 2015 have shown that SGLT2i (–2.66 kg (canagliflozin); –1.81 kg (empagliflozin); –1.80 kg (dapagliflozin) are better than metformin (–1.04 kg) in reducing weight.

Recommendations and statements	CoR	LoE
SGLT2i as a first-line agent may be as effective as metformin in terms of impact on weight	I	A

Impact on Blood Pressure (BP)

Reduction of arterial BP is associated with a reduction of CV morbidity and mortality in patients with T2D.[46] Benefits of SGLT2i include its effect on arterial stiffness, increased glucose excretion alone results in an extra osmotic diuretic impact, and blockage of the cotransporters in the proximal tubule induces a slight rise in sodium urine output (natriuretic effect). Secondly, it has also been suggested that losing weight and reducing sympathetic nervous system activity might lower BP.[47]

Five studies were included in which SGLT2i was directly compared with metformin. Of these five studies, one systematic review and meta-analysis, four RCTs were included.

An RCT conducted by List et al.[5] in 2009 has reported a greater reduction in systolic (–2.6 to –6.4 vs –0.4) and diastolic (–2.6–0.8 vs –0.6) BP in dapagliflozin group when compared to metformin group. In 2013, Ferrannini et al.[6] reported that empagliflozin showed a better reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline. The change from baseline [95% confidence interval (CI)] in SBP for empagliflozin was 0.1 to –1.7 and 2.0 for metformin. The change from baseline (95% CI) in DBP for empagliflozin was –1.6 to –2.2 and –0.6 for metformin. There was a slight increase in the systolic (–3.0–0.5 vs 3.1) and diastolic (–0.1–0.4 vs 1.5) BP in the metformin group when compared to ipragliflozin, based on a study by Fonseca et al.[7] in 2013. The mean change from baseline to 52 weeks was more in both systolic (–3.7 vs –2.4) and diastolic (–0.8 vs –0.2) BP in the ertugliflozin group when compared to metformin as reported by Aronson et al.[8] in 2018. A systematic review and meta-analysis conducted by Pinto et al.[11] in 2015 has shown that SGLT2i is better than metformin in reducing SBP.

Recommendations and statements	CoR	LoE
SGLT2i, as a first-line agent, may be as effective as metformin in terms of impact on BP	I	A

Impact on Lipids

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) has a significant impact on adipose tissue with an increase in lipid mobilization and lipolysis.[48] They reduce insulin concentration, a potent inhibitor of lipolysis, and therefore cause increased lipolysis.[49]

A total of one RCT was included in which SGLT2i was directly compared with metformin.

VERTIS-MONO extension study by Aronson et al.[8] in 2018 reported an increase

in low-density lipoprotein cholesterol (LDL-C) (98.6–101.7 vs 99.7–103.3) and high-density lipoprotein cholesterol (HDL-C) (45.3–46.3 vs 47.4–51.3) levels in the ertugliflozin groups compared with decreased LDL-C (99.2 vs 89.8) and increased HDL-C (45.9 vs 48.2) in the placebo/metformin group, although there was no increase in the LDL-C:HDL-C ratio. SGLT2i causes a modest increase in LDL-cholesterol and HDL-cholesterol, while metformin decreases LDL-C and increases HDL-C.[50,51]

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be as effective as metformin in decreasing LDL-C and increasing HDL-C	II	B

Cardiovascular (CV) Protection

The leading cause of mortality worldwide is CVD,[52] and patients with T2D have a two- to threefold higher risk of developing CVD.[53,54] The cause of mortality in T2D patients is ascribed to CVD in about 40% of cases. Additionally, patients with T2D have a high incidence of nonfatal CV events, with heart failure (HF) hospitalizations making up as much as 33% of these events.[55,56] A recent observational study conducted by Unnikrishnan et al.[57] in 2022 suggested that Indian patients with diabetes had a CVD risk of 15.3 ± 12.3%. Early diagnosis and prevention of CV complications are very important in managing patients with T2D.

Four RCTs were included in which SGLT2i was directly compared with metformin. Eleven important trials conducted on the cardiac protection of SGLT2i are included.

Chen et al.[58] in 2020 suggested that use of SGLT2i has reduced events of HF hospitalization [hazard ratio (HR) 0.47 (95% CI 0.41–0.54, $p < 0.0001$)], acute coronary syndrome (HR 0.50 (95% CI 0.41–0.61, $p < 0.0001$)), and all-cause mortality [HR 0.49 (95% CI 0.44–0.55, $p < 0.0001$)], but increased events of ischemic stroke [HR 1.21 (95% CI 1.10–1.32, $p < 0.0001$)] compared with metformin as first-line treatment. An RCT conducted by Hao et al.[10] in 2022 reported that, when compared to the metformin group, the volume of visceral adipose tissue (associated with cardiometabolic disorders) was also lower in the SGLT2i group. RCT conducted by Deng et al.[36] in 2022 reported that empagliflozin showed HbA1c reduction and improved CVD risk factors. Only individuals receiving empagliflozin showed a drop in BP and uric acid levels and increased hematocrit and adipokine. The considerable improvement in clinical indicators of CVD risk factors in this research indicates that empagliflozin is more helpful to the CV system. Shin et al.,[59] in 2022, conducted an observational study that compared SGLT2i to metformin and reported that patients on SGLT2i had a lower risk for myocardial infarction (HR, 0.70; CI, 0.48–1.00), all-cause mortality (HHF/mortality) (HR, 0.80; CI, 0.66–0.97) and HF hospitalizations (HR, 0.78; CI, 0.63–0.97). A mini-review by Koufakis et al.[60] in 2023 suggested that T2D patients with cardiorenal issues benefit more from SGLT2i.

International Guidelines

American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) Guideline for the Management of Heart Failure, 2022 recommends SGLT2i in patients with T2D as primary prevention for HF, patients with heart failure and reduced ejection fraction (HFrEF), and for patients with heart failure and preserved ejection fraction (HFpEF).[61] The American Diabetes Association (ADA), 2022 standards of care[62] and Expert Consensus Statement, 2020[63] by the ACC suggest using SGLT2i as the first line of treatment for glucose control and high-risk for established heart disease. The Korean Diabetes Association (KDA)[64] in 2021 and the consensus statement by the American Association of Clinical Endocrinologists (AACE)[65] and the American College of Endocrinology in 2020 recommend SGLT2i as initial therapy for individuals with T2D with or at high-risk atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD).

Important Trials: SGLT2i

DELIVER trial ($n = 6,263$) conducted by Peikert et al.[66] in 2022, SOLOIST-WHF study ($n = 1222$) by Bhatt et al.[67] in 2021, EMPEROR-Reduced study ($n = 1,863$) by Packer et al.[68] in 2020, VERTIS CV study ($n = 8,246$) by Cannon et al.[69] in 2020, DECLARE-TIMI ($n = 17,160$) by Wiviott et al.[70] in 2019 and Cahn et al.[71] in 2021, CREDENCE Trial ($n = 4,401$) by Mahaffey et al.[72] in 2019 and EMPA-REG OUTCOME ($n = 7,020$) trial by Zinman et al.[55] in 2015 have shown that treatment with SGLT2i resulted in a significantly lower rate of CV death or hospitalization for HF when compared to placebo. A *post hoc* analysis was performed on EMPA-REG data by Levin et al.[73] in 2020, and it was found that the reduction in risk of CV outcomes with empagliflozin and placebo showed consistent results. Packer et al.,[74] in an EMPEROR-preserved study, suggested that empagliflozin reduced inpatient and outpatient HF events. DAPA HF[75] trial ($n = 4,744$) has reported among patients with HF and a reduced ejection fraction, the risk of worsening HF or death from CV causes was lower among the dapagliflozin group when compared to the placebo.

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may be superior to metformin in providing CV protection in people with CVD and/or HF	I	A

Renal Protection

Renal abnormalities are widespread in T2D, with roughly 50% of patients acquiring some level of renal impairment over time.[76] Many individuals with diabetes already have some degree of renal impairment or abnormalities at diagnosis. As a result, end-stage kidney disease (ESKD), CKD, or both develop over time. SGLT2i work on the extracellular surface of the brush border cell membrane (proximal convoluted tubule—90% of the kidney's reabsorption of glucose), which they reach *via* glomerular filtration and tubular secretion.[77,78] They reduce blood glucose levels and enhance urinary glucose excretion by inhibiting renal glucose reabsorption.

Due to the nonavailability of literature directly comparing SGLT2i with metformin, we have included three systematic review and meta-analysis studies that compared SGLT2i with placebo and seven large trials. RCTs are scarce to evaluate the renoprotective function of metformin monotherapy in patients with T2D. We have included five observational studies and one systematic review.

A systematic review and meta-analysis (27 studies, $n = 7,363$) conducted by Toyama et al.[79] in 2019 has concluded that SGLT2i reduced the annual decline in estimated glomerular filtration rate (eGFR) slope (annual mean difference in kidney function between treatment and control: 1.35 mL/1.73 m^2/year; 95% CI, 0.78–1.93) risk of composite renal outcomes [doubling of serum creatinine (Scr), ESKD, or renal death: HR, 0.71; 95% CI, 0.53–0.95] in patients with T2D and CKD. SGLT2i substantially reduced the risk of dialysis, transplantation, or death due to kidney disease [relative risk (RR) 0.67, 95% CI 0.52–0.86, $p = 0.0019$], reduced ESKD (0.65, 0.53–0·81, $p < 0.0001$), and acute kidney injury (AKI) (0.75, 0.66–0.85, $p < 0.0001$) based on a meta-analysis conducted on important trials.[80] SGLT2i are linked to a notable reduction in adverse renal events, and these benefits are evident even in individuals with an eGFR of <60 mL/minute/1.73 m^2.[81] Zelniker et al.[82] in 2019 conducted a systematic review and meta-analysis and reported that SGLT2i reduced the progression of renal disease by 45% [0.55 (0.48–0.64), $p < 0.0001$] with or without CVD.

In 2016, the United States Food and Drug Administration affirmed the safety of metformin for individuals with mild to moderate kidney impairment (eGFR: 30–60 mL/minute/1.73 m^2), but metformin use is contraindicated in patients with eGFR values < 30 mL/minute/1.73 m^2.[83] Notably, research has highlighted the potential protective qualities of metformin in various conditions, including AKI, CKD, diabetic kidney disease (DKD), autosomal dominant (adult) polycystic kidney disease (ADPKD), lupus nephritis (LN), renal neoplasms, and kidney transplantation.[84–89]

In 2012, Ekström et al.[90] conducted a cohort study involving 51,675 participants from the Swedish National Diabetes Register. The study revealed that among patients with an eGFR ranging from 45 to 60 mL/minute/1.73 m^2, metformin was associated with reduced risks of acidosis/serious infection (adjusted HR 0.85, 95% CI 0.74–0.97) and all-cause mortality (HR 0.87, 95% CI 0.77–0.99). Notably, no heightened risks of all-cause mortality, acidosis/serious infection, or CVD were observed in patients with an eGFR of 30–45 mL/minute/1.73 m^2. Hsu et al.,[91] in their study, concluded that continuous treatment with metformin in patients with moderate CKD and T2D caused a decrease in renal function. Bell et al.[84] in 2017 conducted a large cohort study (n = 25,148) and reported that metformin was associated with a higher rate of survival at 28 days (HR 0.81, 95% CI 0.69, 0.94, p = 0.006) in AKI patients. Metformin was associated with a decreased risk of severe kidney failure based on a cohort study (n = 469,688) by Hippisley-Cox et al.[92] Zhang et al.[93] in 2022 reported that kidney function markers [Scr and blood urea nitrogen (BUN)] were reduced in the metformin group when compared to the control group. A systematic review (17 observational studies) conducted by Crowley et al.[94] in 2017 reported that metformin was associated with reduced all-cause mortality in patients with CKD (eGFR = 30–60 mL/minute/1.73 m^2).

Important Trials: SGLT2i

EMPA-KIDNEY[95] study (n = 6,609) has reported that patients in the empagliflozin group had fewer hospitalizations and reduced composite risk outcomes of kidney disease progression. Heerspink et al.[96] in 2020 conducted a study (DAPA-CKD; n = 4,304) that reported patients on dapagliflozin showed significant reductions in the primary renal composite endpoint (eGFR <50%, ESKD, or renal or CV death) when compared to placebo. CREDENCE trial (n = 4,401) conducted by Perkovic et al.[97] in 2019 in patients with CKD and T2D has shown results similar to DAPA-CKD with a doubling of Scr as an added primary composite endpoint. EMPA-REG OUTCOME (n = 7,020) study by Zinman et al.[55] in 2015 suggested that fewer patients in the empagliflozin group experienced worsening nephropathy due to slower progression to macroalbuminuria. The CANVAS[56] study (n = 10,142) showed similar results, with the progression of albuminuria occurring less frequently with canagliflozin. DECLARE-TIMI 58 study (n = 17,160) by Cahn et al.[71] in 2021 included patients with T2D and multiple CV risk factors. Dapagliflozin was associated with significant decreases in renal composite endpoints and urinary albumin-to-creatinine ratio. According to the EMPEROR-REDUCED trial by Packer et al.[68] in 2020, the annual rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group with less serious renal outcomes. Multiple studies have shown greater declines in eGFR while using SGLT2i,[98,99] and few studies reported no significant changes in eGFR during longer-term treatments.[100]

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be more effective than metformin in people with T2D and CKD	I	A
SGLT2i as a first-line agent may be as effective as metformin in terms of its impact on renal protection	I	C

Antihyperglycemic Combination Therapy

Combination treatment is required to address all pathophysiological routes of T2D and euglycemia since monotherapy alone cannot treat many pathophysiological abnormalities.[101] Additionally, the drug combination should work to restore overall metabolic health rather than just reducing levels of HbA1c. Combination therapy helps target multiple pathways involved in glucose regulation, leading to better glycemic control.

Safe for Combination Therapy with Other Oral Hypoglycemic Agents (OHAS)

The only OHA that specifically targets impaired glucose reabsorption in the kidney, a crucial part of the ominous octet (impaired function of eight organ sets), is SGLT2i.[102] If HbA1c targets are not met after 3 months of monotherapy, the ADA and the European Association for the Study of Diabetes (EASD) advise starting "dual combination therapy" and moving on to "triple combination therapy" if those targets are still not met after 3 months of dual therapy. Furthermore, if the goal HbA1c levels are not reached after 3 months of triple combination treatment, it is advised that insulin (basal or prandial) be administered in addition to the oral glycemic agent.[103]

A total of 23 studies were included: six were RCTs, 12 were systematic reviews and meta-analyses, four were observational studies, and one was a large trial.

Clar et al.[104] (seven RCTs, n = 3,849) in 2012 has shown that combination therapy of dapagliflozin and other OHAs has a better reduction in HbA1c (−0.21 to −0.54%), weight loss (−1.81 to −2.3 kg), than a combination with placebo. When used as a combination therapy, empagliflozin reduced glycemic parameters along with a reduction in CV risk mortality.[105,106] Subgroup analysis of a systematic review conducted by Xu et al.[107] (15 studies) in 2022 reported that compared with placebo, dapagliflozin combined with metformin [mean difference (MD) = −0.45, 95% CI: −0.61 to 0.29, p < 0.00001], insulin (MD = −0.59, 95% CI: −0.83 to −0.36, p < 0.00001), or exenatide (MD = −0.26, 95% CI: −0.53 to 0.01, p < 0.00001) showed a significant reduction in HbA1c levels. With the advent of newer sulfonylureas (SUs), the incidence of hypoglycemic events has reduced. SGLT2i, in combination with SUs, has been shown to lower HBA1c (−0.74 to −0.83%) and other parameters [body weight (−1.8%)], but caution was advised regarding the side effects.[108] The combination of SGLT2i with dipeptidyl peptidase-4 inhibitors (DPP-4i) has better glycemic control with fewer side effects, and a triple therapy along with metformin is preferred.[109,110] This is supported by a systematic review and meta-analysis by Min et al.[111] (seven RCTs, n = 2082) in 2018 and expert opinion by Chadha et al.[112] in 2022. A systematic review and meta-analysis conducted by Li et al.[113] (eight RCTs, n = 1895) in 2022 have concluded that combination therapy of SGLT2i and glucagon-like peptide-1 receptor agonists (GLP-1RA) has a superior effect in reducing HbA1c (0.77–1.75%), BP (SBP: −0.33 mm Hg), lipid values (LDL-C: −23.41 mmol/L). Metformin and SGLT2i complement each other's action, help decrease glycemic parameters and BP, and are well tolerated. This is proved in a systematic review by Kuecker et al.[114] (seven RCTs) in 2016, Jingfan et al.[115] (nine RCTs, n = 2,509) in 2019, Chen et al.[116] (five RCTs, n = 847) in 2019 Gebrie et al.[117] (nine RCTs, n = 10,974) in 2020 and an RCT by Häring et al.[118] in 2014. A systematic review (four RCTs, n = 3749) has shown that the initial dose combination of metformin with SGLT2i has better glycemic reduction benefits than a high dose[119] but with a risk of lactic acidosis and ketoacidosis.[51]

Triple combination therapy of SGLT2i, SU, and metformin has shown favorable

results in achieving the glycemic targets.[120,121] SGLT2i, DPP-4i, and metformin have also shown promising results in reducing blood glucose values.[122–124] Combination with thiazolidinediones has improved glucose levels, but genital mycotic infections (GMIs) were more common.[125]

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may be as safe as metformin for combination therapy with other OHAs	I	A

Safe for Combination with Insulin and Decreased Insulin Requirement

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) is a potential class of drugs for use in conjunction with exogenous insulin. They lower insulin dosage needs, mitigate insulin-induced weight gain, and improve glucose control,[126] but the side effects of SGLT2i should be considered.

A total of 11 studies were included: six were RCTs, one was a systematic review and meta-analysis, two were large trials, and two observational studies were included.

Wilding et al.[127] in 2014 conducted a study for 2 years and reported that dapagliflozin when administered with insulin, reduced the glycemic variables (−0.4%) and weight (0.9–1.4 kg) and stabilized the insulin dose. Inagaki et al., in two studies conducted in 2016[128] and 2018,[129] reported similar results with a decrease in insulin dose and glycemic parameters when compared to a placebo. Neal et al.[130] in 2017 (CANVAS trial) suggested a reduction in HbA1c (−0.58 to −0.73%) along with insulin dose and body weight, supported by other studies.[127,131] An RCT conducted by Sone et al.[132] in 2020 suggested that empagliflozin, when given along with insulin, reduced HbA1c (0.92–1.00%), FBS (–27.62 mg/dL to –21.99 mg/dL), body weight (–1.78 to –1.92 kg), and insulin dose compared to placebo. Similar results were also seen in studies conducted by Rosenstock et al.[133] in 2014 (EMPA-REG MDI trial) and Rosenstock et al.[131] in 2015 (EMPA-REG BASALTM trial). Kanazawa et al.[134] in 2019 conducted an RCT in which patients were divided into the insulin and the insulin+dapagliflozin groups. It was observed that patients on both insulin and dapagliflozin had a higher rate of euglycemia; the total daily dose of insulin was 19% lower. Wehrman et al.[135] in 2022 reported that patients who received multiple daily insulin injections when added with SGLT2i showed a 2.45-unit reduction in basal insulin and a 7.12-unit reduction in short-acting insulin along with a significant reduction in HbA1c and weight. A study conducted by Jiang et al.[136] in 2022 included 62 patients who were given dapagliflozin as an adjunct to insulin. Patients on dapagliflozin and insulin demonstrated a significant decrease in the MAGE (6.25 ± 2.55 vs 2.34 ± 1.10) and improved insulin sensitivity (reduction in HOMA-IR and increase in HOMA-B) compared to insulin alone. A systematic review and meta-analysis of RCTs (n = 3,069) conducted by Yang et al.[137] in 2017 reported that when SGLT2i was given along with insulin, it helped reduce HbA1c (MD: 1.35%, 95% CI [–2.36 to –0.34], p=0.009)], weight [MD –2.30kg, 95%CI (–3.09 to –1.50), p< 0.00001], BP, the total dosage of insulin [MD –4.85U/24hours, 95%CI (–7.42 to –2.29), p= 0.002], and FPG [MD –1.01 mmol/L, 95%CI (–1.98 to 0.04), p= 0.04], with an increase in hypoglycemia and urinary tract infections, compared to the control group.

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may be as safe as metformin in combination with insulin	I	A
SGLT2i as a first-line agent may be as effective as metformin in decreasing insulin requirement	I	A

Safety

Identification of predisposing or precipitating risk factors that might assist in preventing the most severe problems is a crucial component while assessing the patient. The overall CV and renal advantages are unaffected by adverse events. The safety profile of SGLT2i is good, and the risk of adverse events is rare.

Low Risk of Hypoglycemia

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) only lowers plasma glucose levels by preventing the reabsorption of filtered glucose, which decreases as plasma glucose levels fall. As a result, in the absence of hypoglycemia-causing therapies, they seldom induce hypoglycemia.[138] In T2D patients, SGLT2i enhances plasma glucagon concentrations and gluconeogenesis. As a result, the risk of hypoglycemia with SGLT2i is minimal.[25,139] The risk of hypoglycemia with SGLT2i is low unless coadministered with insulin and other anti-diabetic drugs (sulphonylurea, α-glucosidase, etc.).[140–143] As a result, when taken with an SGLT2i, the dose of insulin and/or insulin secretagogues may need to be lowered to avoid hypoglycemia.

A total of six studies were included in which SGLT2i was directly compared with metformin. Of these six studies, one systematic review and meta-analysis, five RCTs were included.

In a study by List et al.[5] in 2009, hypoglycemia was reported in 6–10% of patients on dapagliflozin (dose independent), 4% of placebo-treated patients, and 9% of metformin-treated patients. In a study conducted by Fonseca et al.[7] in 2013, hypoglycemia events were observed in two out of 135 patients on Ipragliflozin, while zero events were reported in the metformin and placebo groups. Ferrannini et al.,[6] in 2013, also conducted a study that reported empagliflozin (three events) showing slightly higher episodes of hypoglycemia when compared to metformin (two events). Hypoglycemic events were slightly low in the ertugliflozin group (1.3–2.6%) compared to the placebo/metformin group (4.6%) in a study conducted by Aronson et al.[8] in 2018. Hao et al.[10] in 2022 reported that hypoglycemia was low both in the canagliflozin and metformin groups. A systematic review and meta-analysis conducted by Storgaard et al.[144] (34 RCTs, n = 9,154) in 2016 reported that SGLT2i was associated with an increased risk of nonsevere hypoglycemia compared to metformin.

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be as effective as metformin in lowering the risk of hypoglycemia	I	A

Adverse Drug and Side Effects

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) has many beneficial effects, though there are some risks as well. Clinicians should verify the patient's bone density, review their cardiac profile, and evaluate their hepatic and renal function before beginning them on SGLT2i medication.[145]

A total of six studies were included in which SGLT2i was directly compared with metformin. Of these six studies, five RCTs and one cohort study were included.

Reported urinary tract infections in the dapagliflozin, placebo, and metformin groups are 5–12, 6, and 9%, respectively, as reported by List et al.[5] Genital infections also were slightly more in the dapagliflozin (2–7%) compared to metformin (2%) while hypotensive events were more in the metformin group (4 vs 0–2%). In a study carried out by Fonseca et al.[7] in 2013, it was found that drug-related adverse events were similar in ipragliflozin (11.4–25.4%), placebo (24.6%), and metformin (18.8%) groups. Ferrannini et al.,[6] in their study, concluded that, in the empagliflozin groups, the incidence of investigator-defined drug-related adverse effects (11.9–13.2%) was higher compared to the metformin group (7.1%). Adverse events resulted in discontinuation for 0.9–4.7%

of patients in the empagliflozin groups and 1.8% of patients receiving metformin. Hypoglycemic events were documented in 0.9–2.4% of patients using empagliflozin and 3.6% of those on metformin monotherapy. Incidents consistent with urinary tract infections were reported in 3.8–6.4% of patients on empagliflozin monotherapy and 3.6% on metformin monotherapy. Genital infections occurred more frequently with empagliflozin (3.0–5.5%) than with metformin monotherapy (1.8%). GMIs were slightly more common in females than males; in a study conducted by Aronson et al.,[8] the ertugliflozin group had a slightly higher incidence of GMI than metformin. Hypovolemia was more in the placebo/metformin (4.6%) group than ertugliflozin (1.9–2%). Genital infections were also reported more in SGLT2i (HR, 2.19; CI, 1.91–2.51) compared to metformin in a study by Shin et al.[59] Hao et al.[10] in 2022 reported that patients on canagliflozin had a higher rate of GMI (three cases) than metformin (one case). The overall adverse events rate was slightly higher in the canagliflozin group (8.7 vs 6.8%).

Recommendations and statements	*CoR*	*LoE*
SGLT2i, as a first-line agent, may have greater chances of genital infections compared to metformin and should be used cautiously	I	A

Cost-effectiveness

Patients with diabetes are more likely to develop macrovascular or microvascular complications. As a result, individuals are frequently and exhaustively confronted with healthcare systems. Diabetes treatment and its related consequences impose a massive economic burden on both the family and national levels. In a developing country like India, most diabetes patients face substantial out-of-pocket costs.[146] The most generally reported costing elements were direct cost items[147] (expenditure on medications, diagnostic expenditures, transportation cost, hospitalization, and consultation fee) and indirect cost items (wage loss, health class spending, and trip expenditure).[148] The majority of the research on the cost of diabetes identified "drugs" as the most significant cost component.[146] The International Diabetes Federation (IDF) reported that the total diabetes-related health cost (United States dollar) in India for individuals (20–79 years) with diabetes in 2021 is up to 10 billion.[149]

Four studies were included in which SGLT2i was directly compared with metformin. Of these four studies, one was a systematic review, one was a meta-analysis, and two observational studies were included.

To compare the cost-effectiveness of empagliflozin to conventional care in preventing CV morbidity and death in T2D patients, a Markov model was developed by Nguyen et al.[150] in 2018. A study conducted in China by Cai et al.[151] in 2019, based on the Cardiff diabetes model and meta-analysis from the 71 clinical trials, reported that treatment with dapagliflozin (8,626 Chinese Yuan) was more cost-effective than metformin. Therapy with dapagliflozin resulted in 0.8 more quality-adjusted life years (QALYs) than metformin. A study conducted by Nian et al.[152] in 2020 reported that dapagliflozin was more costly and produced fewer health benefits when compared to metformin. A systematic review of 24 studies conducted by Yoshida et al.[153] in 2020 suggested that SGLTi are cost-effective compared to metformin/standard care. Based on total lifetime treatment costs, QALYs, and incremental cost-effectiveness ratios (ICERs), empagliflozin might be cost-effective compared to standard treatment in T2D patients at high CV risk.

Recommendations and statements	*CoR*	*LoE*
SGLT2i as a first-line agent may be as cost-effective as metformin for treating patients with T2D in India	I	A

Discussion

While the clinical and scientific communities progress to map the boundaries of the pathophysiology and complications of T2D, more and more people across the globe are constantly adding themselves to this group. A lot of progress may have occurred in our understanding of the disease, but its direct impact on the reduction of morbidity and mortality is yet to be realized. Prevention, reversal, management, and prevention of diabetes-specific complications are definite priorities in managing diabetes, but the growing burden of obesity, CV, and renal events, especially in populations at risk, such as Indians, is still a significant concern that needs a serious address.

The choice of first-line therapy may be a clinical decision based on the segmented pathophysiology of the disease, but it must consider the patient as a whole and provide the best possible management that mitigates the disease while promoting the overall health and general well-being of the patient. By undertaking a methodical, systematic literature search and review, the authors have discussed the suitability of SGLT2i on various aspects of the first-line of therapy of T2D based on glycemic control, management of diabetes, management of diabetes-related complications, combination therapy, safety, and cost-effectiveness. This analysis summarizes that SGLT2i may be considered to be noninferior to metformin on parameters related to the pathophysiology of diabetes, but additionally, they bring with them superior qualities pertaining especially to CV and renal protection. The methods of this paper are purely qualitative. Quantitative analysis will have to be summarized to claim the noninferiority. However, this qualitative evidence synthesis comprehensively summarizes available literature and irrevocably advocates the noninferiority of SGLT2i against metformin.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) had a significant impact on glycemic control with a reduction in HbA1c and postlunch glucose levels and by reducing GV. They do not have a role in insulin secretion, but they preserve β-cell function, increase insulin sensitivity, and reduce insulin resistance. Apart from glycemic control, SGLT2i helps reduce weight, BP, and lipid levels. SGLT2i is far superior when compared to metformin due to its cardiorenal protection. In India, these are extremely important aspects of first-line therapy (patients with T2D), as the risk factors for T2D impact cardiac and renal disorders (Table 3).

The cardiorenal protection potential of SGLT2i in the general population also shifts the paradigm in the concept of first-line therapy by SGLT2i. The ADA, KDA, and AACE associations strongly suggest using SGLT2i as initial therapy for T2D patients with high-risk cardiac and renal disorders. The authors strongly recommend using SGLT2i for this cohort of patients in India as the risk of cardiac and renal disorders in patients with diabetes occurs more prematurely. Our analysis also shows that they are safe to use in combination therapy with other oral antihyperglycemic drugs and insulin, but care must be taken to adjust the dosage of other drugs to prevent hypoglycemia complications.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) has a good safety profile that is noninferior to metformin and has rare side effects (genitourinary tract infection, ketoacidosis, amputations, fractures). The balance between risk and benefits should be considered before the initiation of SGLT2i on a case-to-case basis. SGLT2i is as cost-effective as metformin, even more so with the availability of generic drugs in India.

Delayed achievement of HbA1c goals in newly diagnosed patients with T2D is related to an increased long-term risk of acquiring CVD, a phenomenon known as the legacy

Table 3: Recommendations, CoR, and LoE for each domain

Topic	*Domain*		*Recommendations and statements*	*CoR*	*LoE*
Glycemic control	1.1	Impact on HbA1c	SGLT2i can be considered a first-line in the management of T2D than metformin based on its impact on HbA1c	I	A
	1.2	GV	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on GV	I	C
Extraglycemic effect	2.1	β-cell function	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on β cell function	I	C
	2.2	Insulin resistance	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on insulin sensitivity	I	A
	2.3	Gut microbiome	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on gut microbiome	II	B
	2.4	Impact on weight	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on weight	I	A
	2.5	Impact on BP	SGLT2i as a first-line agent may be as effective as metformin in terms of impact on BP	I	A
	2.6	Impact on lipids	SGLT2i as a first-line agent may be as effective as metformin in decreasing LDL-C and increasing HDL-C	II	B
	2.7	CV protection	SGLT2i as a first-line agent may be superior to metformin in providing CV protection in people with CVD and/or HF	I	A
	2.8	Renal protection	SGLT2i as a first-line agent may be more effective than metformin in people with T2D and CKD	I	A
			SGLT2i as a first-line agent may be as effective as metformin in terms of its impact on renal protection	I	C
Antihyperglycemic combination therapy	3.1	Safe for combination therapy with other OHAs	SGLT2i as a first-line agent may be as safe as metformin for combination therapy with other OHAs	I	A
	3.2	Safe for combination with insulin and decreases insulin requirement	SGLT2i, as a first-line agent, may be as safe as metformin in combination with insulin	I	A
			SGLT2i as a first-line agent may be as effective as metformin in decreasing insulin requirement	I	A
Safety	4.1	Low risk of hypoglycemia	SGLT2i as a first-line agent may be as effective as metformin in lowering the risk of hypoglycemia	I	A
	4.2	Adverse drug and side effects	SGLT2i, as a first-line agent, may have greater chances of genital infections as compared to metformin and should be used cautiously	I	A
Cost-effectiveness	5	Cost-effectiveness	SGLT2i as a first-line agent may be as cost-effective as metformin for treating patients with T2D in India	I	A

effect. When SGLT-2i was introduced in the first 2 years, this association was no longer evident, indicating that these medications minimize the occurrence of the legacy effect. Early therapy with these medications may potentially have a long-term advantage in people who do not achieve optimal glycemic control following T2D diagnosis.[154]

Conclusion

Given the growing emphasis on preventing risks in individuals diagnosed with diabetes, renewed attention is focused on finding an initial treatment option to complement the current preferred first-line agent, metformin. SGLT2i have been extensively studied and can potentially serve as the primary choice for people recently diagnosed with diabetes, even when other associated health issues are not yet evident during the early stages of the condition. This article identifies various scientific aspects that should be considered when considering a primary treatment for T2D. It also provides an unbiased summary of the available research findings in these areas, directly comparing SGLT2i with metformin in relation to specific outcomes relevant to these different aspects. In cases where no direct studies were comparing SGLT2i with metformin, studies comparing SGLT2i with placebo were taken into consideration. The recommendations provided in this article are rooted in evidence-based practices and are further supported by a consensus-based recommendation system. In conclusion, this article recommends using SGLT2i as the first-line treatment option for managing newly diagnosed T2D patients in India.

Acknowledgments

We acknowledge Dr Ashish Birla, Dr Ashish Prasad, and Dr Smriti Gadia from USV Pvt Ltd for their assistance in the conduct of the project. Dr Raghunath Dantu and Dr Uday Pratap Singh from MEDEVA provided literature search support, evidence synthesis, and medical writing support.

Authors Declaration

Supplementary tables are available with corresponding author and can be provided whenever required.

References

1. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol 2021;69(11):2932–2938.
2. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, et al. Type 2 diabetes and cardiovascular disease: have all risk factors the same strength? World J Diabetes 2014;5(4):444–470.
3. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41(12):2669–2701.
4. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management

of arterial hypertension of the European Society of Hypertension endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens 2023;41(12):1874–2071.
5. List JF, Woo V, Morales E, et al. Sodium-glucose cotransport inhibition with dapagliflozin in Type 2 diabetes. Diabetes Care 2009;32(4):650–657.
6. Ferrannini E, Berk A, Hantel S, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care 2013;36(12):4015–4021.
7. Fonseca VA, Ferrannini E, Wilding JP, et al. Active- and placebo-controlled dose-finding study to assess the efficacy, safety, and tolerability of multiple doses of ipragliflozin in patients with type 2 diabetes mellitus. J Diabetes Complications 2013;27(3):268–273.
8. Aronson R, Frias J, Goldman A, et al. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes Obes Metab 2018;20(6):1453–1460.
9. Shibuya T, Fushimi N, Kawai M, et al. Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: a prospective randomized controlled pilot study. Diabetes Obes Metab 2018;20(2):438–442.
10. Hao Z, Sun Y, Li G, et al. Effects of canagliflozin and metformin on insulin resistance and visceral adipose tissue in people with newly-diagnosed type 2 diabetes. BMC Endocr Disord 2022;22(1):37.
11. Pinto LC, Rados DV, Remonti LR, et al. Efficacy of SGLT2 inhibitors in glycemic control, weight loss and blood pressure reduction: a systematic review and meta-analysis. Diabetol Metab Syndr 2015;7(Suppl 1):A58.
12. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? Diabetes Metab J 2015;39(4):273–282.
13. Makris K, Spanou L. Is there a relationship between mean blood glucose and glycated hemoglobin? J Diabetes Sci Technol 2011;5(6):1572–1583.
14. Nishimura R, Tanaka Y, Koiwai K, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. Cardiovasc Diabetol 2015;14(1):11.
15. Li FF, Gao G, Li Q, et al. Influence of dapagliflozin on glycemic variations in patients with newly diagnosed type 2 diabetes mellitus. J Diabetes Res 2016;2016:5347262.
16. Erickson ML, Little JP, Gay JL, et al. Postmeal exercise blunts postprandial glucose excursions in people on metformin monotherapy. J Appl Physiol 2017;123(2):444–450.
17. Lu J, Zang J, Li H. Impact of three oral antidiabetic drugs on markers of β-cell function in patients with type 2 diabetes: a meta-analysis. PLOS ONE 2013;8(10):e76713.
18. Tura A, Pacini G, Kautzky-Willer A, et al. Basal and dynamic proinsulin-insulin relationship to assess beta-cell function during OGTT in metabolic disorders. Am J Physiol Endocrinol Metab 2003;285(1):E155–E162.
19. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27(6): 1487–1495.
20. Standl E. The importance of beta-cell management in type 2 diabetes. Int J Clin Pract Suppl 2007;153:10–19.
21. Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab 2013;15(12):1136–1145.
22. Kutoh E, Wada A, Murayama T, et al. Two glucose-lowering mechanisms of canagliflozin depending on body weight changes in drug-naïve subjects with type 2 diabetes. Drugs R D 2018;18(4):309–315.
23. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013;15(4): 372–382.
24. Kutoh E, Wada A, Murayama T, et al. Characterization of metabolic parameters in responders and nonresponders treated with canagliflozin monotherapy in drug-naive subjects with type 2 diabetes. Indian J Endocrinol Metab 2018;22(2):185–190.
25. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124(2):499–508.
26. Polidori D, Mari A, Ferrannini E. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves model-based indices of beta cell function in patients with type 2 diabetes. Diabetologia 2014;57(5):891–901.
27. U.K. Prospective Diabetes Study Group 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44(11):1249–1258.
28. Kahn SE, Lachin JM, Zinman B, et al. Effects of rosiglitazone, glyburide, and metformin on β-cell function and insulin sensitivity in adopt. Diabetes 2011;60(5):1552–1560.
29. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) group. JAMA 1999;281(21):2005–2012.
30. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977–986.
31. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352(9131):854–865.
32. Xu B, Li S, Kang B, et al. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. Cardiovasc Diabetol 2022;21(1):83.
33. Muniyappa R, Lee S, Chen H, et al. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab 2008;294(1):E15–E26.
34. Fakhrolmobasheri M, Abhari AP, Manshaee B, et al. Effect of sodium–glucose cotransporter 2 inhibitors on insulin resistance; a systematic review and meta-analysis. Acta Diabetol 2023;60(2):191–202.
35. Carding S, Verbeke K, Vipond DT, et al. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 2015;26:26191.
36. Deng X, Zhang C, Wang P, et al. Cardiovascular benefits of empagliflozin are associated with gut microbiota and plasma metabolites in type 2 diabetes. J Clin Endocrinol Metab 2022;107(7):1888–1896.
37. Forslund K, Hildebrand F, Nielsen T, et al. Disentangling the effects of type 2 diabetes and metformin on the human gut microbiota. Nature 2015;528(7581):262–266.
38. Tong X, Xu J, Lian F, et al. Structural alteration of gut microbiota during the amelioration of human type 2 diabetes with hyperlipidemia by metformin and a traditional Chinese herbal formula: a multicenter, randomized, open label clinical trial. mBio 2018;9(3):e02392–e02317.
39. Wu H, Esteve E, Tremaroli V, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med 2017;23(7):850–858.
40. Mueller NT, Differding MK, Zhang M, et al. Metformin affects gut microbiome composition and function and circulating short-chain fatty acids: a randomized trial. Diabetes Care 2021;44(7):1462–1471.
41. van Bommel EJM, Herrema H, Davids M, et al. Effects of 12-week treatment with dapagliflozin and gliclazide on faecal microbiome: results of a double-blind randomized trial in patients with type 2 diabetes. Diabetes Metab 2020;46(2):164–168
42. Leitner DR, Frühbeck G, Yumuk V, et al. Obesity and type 2 diabetes: two diseases with a need for combined treatment strategies - EASO can lead the way. Obes Facts 2017;10(5):483–492.
43. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2(SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs 2015;75(1):33–59.
44. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2(SGLT2) inhibitor, in diabetes mellitus. Cardiovasc Diabetol 2015;14:142.
45. Janež A, Fioretto P. SGLT2 inhibitors and the clinical implications of associated weight loss in type 2 diabetes: a narrative review. Diabetes Ther 2021;12(8):2249–2261.
46. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321(7258):412–419.
47. van Baar MJB, van Ruiten CC, Muskiet MHA, et al. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care 2018;41(8):1543–1556.
48. Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab 2016;18(8): 783–794.
49. Søndergaard E, Espinosa De Ycaza AE, Morgan-Bathke M, et al. How to measure adipose tissue insulin sensitivity. J Clin Endocrinol Metab 2017;102(4): 1193–1199.
50. Sánchez-García A, Simental-Mendía M, Millán-Alanís JM, et al. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: a systematic review and meta-analysis of 48 randomized controlled trials. Pharmacol Res 2020;160:105068.
51. Donnan K, Segar L. SGLT2 inhibitors and metformin: dual antihyperglycemic therapy and the risk of metabolic acidosis in type 2 diabetes. Eur J Pharmacol 2019;846:23–29.
52. Ritchie H, Spooner F, Roser M. Causes of death. Our World in Data [Internet]. 2018 Feb 14 [cited 2023 May 2]; Available from: https://ourworldindata.org/causes-of-death
53. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332(7533):73–78.
54. Emerging Risk Factors Collaboration,Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375(9733):2215–2222.
55. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117–2128.
56. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644–657.
57. Unnikrishnan AG, Sahay RK, Phadke U, et al. Cardiovascular risk in newly diagnosed type 2 diabetes patients in India. PLOS ONE 2022;17(3):e0263619.
58. Chen TH, Li YR, Chen SW, et al. Sodium-glucose cotransporter 2 inhibitor versus metformin as first-line therapy in patients with type 2 diabetes mellitus: a multi-institution database study. Cardiovasc Diabetol 2020;19(1):189.
59. Shin H, Schneeweiss S, Glynn RJ, et al. Cardiovascular outcomes in patients initiating first-line treatment of type 2 diabetes with sodium–glucose cotransporter-2 inhibitors versus metformin. Ann Intern Med 2022;175(7):927–937.
60. Koufakis T, Papazafiropoulou A, Makrilakis K, et al. Sodium-glucose co-transporter 2 inhibitors versus metformin as the first-line treatment for type 2 diabetes: is it time for a revolution? Cardiovasc Drugs Ther 2023;37(2):315–321.

61. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation 2022;145(18):e895–e1032.
62. American Diabetes Association. Standards of medical care in diabetes—2022 abridged for primary care providers. Clinical Diabetes 2022;40(1):10–38.
63. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes; a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2020;76(9):1117–1145.
64. Hur KY, Moon MK, Park JS, et al. 2021 clinical practice guidelines for diabetes mellitus in Korea. Diabetes Metab J 2021;45(4):461–481.
65. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American association of clinical endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2020 executive summary. Endocr Pract 2020;26(1):107–139.
66. Peikert A, Martinez FA, Vaduganathan M, et al. Efficacy and safety of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to age: The DELIVER trial. Circ Heart Fail 2022;15(10):e010080.
67. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384(2):117–128.
68. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413–1424.
69. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383(15):1425–1435.
70. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347–357.
71. Cahn A, Raz I, Leiter LA, et al. Cardiovascular, renal, and metabolic outcomes of dapagliflozin versus placebo in a primary cardiovascular prevention cohort: analyses from DECLARE-TIMI 58. Diabetes Care 2021;44(5):1159–1167.
72. Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. Circulation 2019;140(9):739–750.
73. Levin A, Perkovic V, Wheeler DC, et al. Empagliflozin and cardiovascular and kidney outcomes across KDIGO risk categories: post hoc: analysis of a randomized, double-blind, placebo-controlled, multinational trial. Clinical J Am Soc Nephrol 2020;15(10):1433–1444.
74. Packer M, Butler J, Zannad F, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-preserved trial. Circulation 2021;144(16):1284–1294.
75. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995–2008.
76. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol 2016;12(2):73–81.
77. Fu Y, Breljak D, Onishi A, et al. Organic anion transporter OAT3 enhances the glucosuric effect of the SGLT2 inhibitor empagliflozin. Am J Physiol Renal Physiol 2018;315(2):F386–F394.
78. Ghezzi C, Hirayama BA, Gorraitz E, et al. SGLT2 inhibitors act from the extracellular surface of the cell membrane. Physiol Rep 2014;2(6):e12058.
79. Toyama T, Neuen BL, Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. Diabetes Obes Metab 2019;21(5):1237–1250.
80. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;7(11):845–854.
81. Lo KB, Gul F, Ram P, et al. The effects of SGLT2 inhibitors on cardiovascular and renal outcomes in diabetic patients: a systematic review and meta-analysis. Cardiorenal Med 2020;10(1):1–10.
82. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393(10166):31–39.
83. Lipska KJ, Flory J, Hennessy S, et al. Modifying prescribing guidelines by petitioning the FDA: the metformin experience. Circulation 2016;134(18): 1405–1408.
84. Bell S, Farran B, McGurnaghan S, et al. Risk of acute kidney injury and survival in patients treated with metformin: an observational cohort study. BMC Nephrol 2017;18(1):163.
85. Neven E, Vervaet B, Brand K, et al. Metformin prevents the development of severe chronic kidney disease and its associated mineral and bone disorder. Kidney Int 2018;94(1):102–113.
86. Ravindran S, Kuruvilla V, Wilbur K, et al. Nephroprotective effects of metformin in diabetic nephropathy. J Cell Physiol 2017;232(4):731–742.
87. Tan MKX, Heng TYJ, Mak A. The potential use of metformin, dipyridamole, n-acetylcysteine and statins as adjunctive therapy for systemic lupus erythematosus. Cells 2019;8(4):323.
88. Tseng CH. Use of metformin and risk of kidney cancer in patients with type 2 diabetes. Eur J Cancer 2016;52:19–25.
89. Stephen J, Anderson-Haag TL, Gustafson S, et al. Metformin use in kidney transplant recipients in the United States: an observational study. Am J Nephrol 2014;40(6):546–553.
90. Ekström N, Schiöler L, Svensson AM, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012;2(4):e001076.
91. Hsu WH, Hsiao PJ, Lin PC, et al. Effect of metformin on kidney function in patients with type 2 diabetes mellitus and moderate chronic kidney disease. Oncotarget 2017;9(4):5416–5423.
92. Hippisley-Cox J, Coupland C. Diabetes treatments and risk of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia: open cohort study in primary care. BMJ 2016;352:i1450.
93. Zhang Z, Dong H, Chen J, et al. Effects of metformin on renal function, cardiac function, and inflammatory response in diabetic nephropathy and its protective mechanism. Dis Markers 2022;2022:e8326767.
94. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 2017;166(3):191–200.
95. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388(2):117–127.
96. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436–1446.
97. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295–2306.
98. Kashiwagi A, Takahashi H, Ishikawa H, et al. A randomized, double-blind, placebo-controlled study on long-term efficacy and safety of ipragliflozin treatment in patients with type 2 diabetes mellitus and renal impairment: results of the long-term ASP1941 safety evaluation in patients with type 2 diabetes with renal impairment (LANTERN) study. Diabetes Obes Metab 2015;17(2):152–160.
99. Kohan DE, Fioretto P, Johnsson K, et al. The effect of dapagliflozin on renal function in patients with type 2 diabetes. J Nephrol 2016;29(3):391–400.
100. Ji L, Ma J, Li H, et al. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clin Ther 2014;36(1):84–100.e9.
101. DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;36(Suppl 2):S127–S138.
102. Vivian EM. Sodium-glucose co-transporter 2(SGLT2) inhibitors: a growing class of antidiabetic agents. Drugs Context 2014;3:212264.
103. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38(1):140–149.
104. Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2(5):e001007.
105. Hershon KS. Options for empagliflozin in combination therapy in type 2 diabetes mellitus. Int J Gen Med 2016;9:155–712.
106. Romera I, Gomis R, Crowe S, et al. Empagliflozin in combination with oral agents in young and overweight/obese Type 2 diabetes mellitus patients: A pooled analysis of three randomized trials. J Diabetes Complications 2016;30(8):1571–1576.
107. Xu X, Xu W, Zhuo Q, et al. The efficacy and safety of dapagliflozin combined with oral hypoglycemic agents in patients with type 2 diabetes: a systematic review and meta-analysis. Ann Palliat Med 2022;11(3):1028–1037.
108. Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin used in conjunction with sulfonylurea in patients with type 2 diabetes mellitus: a randomized, controlled trial. Diabetes Ther 2015;6(3):289–302.
109. Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert Opin Drug Metab Toxicol 2016;12(12):1407–1417.
110. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 2015;38(3):376–383.
111. Min SH, Yoon JH, Moon SJ, et al. Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis. Sci Rep 2018;8(1):4466.
112. Chadha M, Das AK, Deb P, et al. Expert opinion: optimum clinical approach to combination-use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Ther 2022;13(5):1097–1114.
113. Li C, Luo J, Jiang M, et al. The efficacy and safety of the combination therapy with GLP-1 receptor agonists and SGLT-2 Inhibitors in type 2 diabetes mellitus: a systematic review and meta-analysis. Front Pharmacol 2022:13:838277.
114. Kuecker CM, Vivian EM. Patient considerations in type 2 diabetes – role of combination dapagliflozin–metformin XR. Diabetes Metab Syndr Obes 2016;9: 25–35.
115. Jingfan Z, Ling L, Cong L, et al. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus with inadequate glycemic control on metformin: a meta-analysis. Arch Endocrinol Metab 2019;63(5):478–486.
116. Chen W, Li P, Wang G, et al. Efficacy and safety of ipragliflozin as add-on to metformin for type 2 diabetes: a meta-analysis of double-blind randomized controlled trials. Postgrad Med 2019;131(8):578–588.
117. Gebrie D, Getnet D, Manyazewal T. Cardiovascular safety and efficacy of metformin-SGLT2i versus metformin-sulfonylureas in type 2 diabetes:

systematic review and meta-analysis of randomized controlled trials. Sci Rep 2021;11(1):137.
118. Häring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014;37(6):1650–1659.
119. Milder TY, Stocker SL, Abdel Shaheed C, et al. Combination therapy with an SGLT2 Inhibitor as initial treatment for type 2 diabetes: a systematic review and meta-analysis. J Clin Med 2019;8(1):45.
120. Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2(SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab 2013;15(12):1154–1160.
121. Matthaei S, Bowering K, Rohwedder K, et al. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care 2015;38(3):365–372.
122. Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2014;37(3):740–750.
123. Tinahones FJ, Gallwitz B, Nordaby M, et al. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: two 24-week randomized, double-blind, double-dummy, parallel-group trials. Diabetes Obes Metab 2017;19(2):266–274.
124. Mathieu C, Catrinoiu D, Ranetti AE, et al. Characterization of the open-label lead-in period of two randomized controlled phase 3 trials evaluating dapagliflozin, saxagliptin, and metformin in type 2 diabetes. Diabetes Ther 2018;9(4):1703–1711.
125. Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-C trial. Diabetes Obes Metab 2014;16(2):147–158.
126. DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab 2012;14(1):5–14.
127. Wilding JP, Woo V, Rohwedder K, et al. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Diabetes Obes Metab 2014;16(2):124–136.
128. Inagaki N, Harashima S, Maruyama N, et al. Efficacy and safety of canagliflozin in combination with insulin: a double-blind, randomized, placebo-controlled study in Japanese patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2016;15:89.
129. Inagaki N, Harashima SI, Kaku K, et al. Long-term efficacy and safety of canagliflozin in combination with insulin in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab 2018;20(4):812–820.
130. Neal B, Perkovic V, de Zeeuw D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care 2015;38(3):403–411.
131. Rosenstock J, Jelaska A, Zeller C, et al. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab 2015;17(10):936–948.
132. Sone H, Kaneko T, Shiki K, et al. Efficacy and safety of empagliflozin as add-on to insulin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab 2020;22(3):417–426.
133. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care 2014;37(7):1815–1823.
134. Kanazawa K, Uchino H, Shigiyama F, et al. Sustained fasting glucose oxidation and postprandial lipid oxidation associated with reduced insulin dose in type 2 diabetes with sodium–glucose cotransporter 2 inhibitor: a randomized, open-label, prospective study. J Diabetes Investig 2019;10(4):1022–1031.
135. Wehrman G, Halton M, Riveland B, et al. Comparison of A1c reduction, weight loss, and changes in insulin requirements with addition of GLP-1 agonists vs SGLT-2 inhibitors in patients using multiple daily insulin injections. J Pharm Pract 2022:8971900221134174.
136. Jiang LL, Zhang P, Liu BL, et al. Effects of dapagliflozin adjunct to insulin on glycemic variations in patients with newly diagnosed type 2 diabetes: a randomized, controlled, open-labeled trial. Biomed Res Int 2021;2021:6618257.
137. Yang Y, Chen S, Pan H, et al. Safety and efficiency of sglt2 inhibitor combining with insulin in subjects with diabetes: systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017;96(21):e6944.
138. DeSantis A, Nathan DM, Mulder JE. Sodium-glucose co-transporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus. 2021;2.
139. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124(2):509–514.
140. Li J, Shao YH, Wang XG, et al. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors as add-on to metformin and sulfonylurea treatment for the management of type 2 diabetes: a meta-analysis. Endocr J 2018;65(3):335–344.
141. Yabe D, Yasui A, Ji L, et al. Safety and tolerability of empagliflozin in East Asian patients with type 2 diabetes: Pooled analysis of phase I–III clinical trials. J Diabetes Investig 2019;10(2):418–428.
142. Committee on the Proper Use of SGLT2 Inhibitors. Recommendations on the proper use of SGLT2 inhibitors. J Diabetes Investig 2020;11(1):257–261.
143. Cai X, Gao X, Yang W, et al. No disparity of the efficacy and all-cause mortality between Asian and non-Asian type 2 diabetes patients with sodium–glucose cotransporter 2 inhibitors treatment: a meta-analysis. J Diabetes Investig 2018;9(4):850–861.
144. Storgaard H, Gluud LL, Bennett C, et al. Benefits and harms of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: a systematic review and meta-analysis. PLoS One 2016;11(11):e0166125.
145. Pittampalli S, Upadyayula S, Mekala HM, et al. Risks vs benefits for SGLT2 inhibitor medications. Fed Pract 2018;35(7):45–48.
146. Oberoi S, Kansra P. Economic menace of diabetes in India: a systematic review. Int J Diabetes Dev Ctries 2020;40(4):464–475.
147. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36 (Suppl 1):S67–S74.
148. Bansode B, Jungari DS. Economic burden of diabetic patients in India: a review. Diabetes Metab Syndr 2019;13(4):2469–2472.
149. Federation ID. IDF Diabetes Atlas, tenth International Diabetes. 2021;
150. Nguyen E, Coleman CI, Nair S, et al. Cost-utility of empagliflozin in patients with type 2 diabetes at high cardiovascular risk. J Diabetes Complications 2018;32(2):210–215.
151. Cai X, Shi L, Yang W, et al. Cost-effectiveness analysis of dapagliflozin treatment versus metformin treatment in Chinese population with type 2 diabetes. J Med Econ 2019;22(4):336–343.
152. Nian H, Wan X, Ma J, et al. Economic evaluation of dapagliflozin versus metformin in Chinese patients whose diabetes is inadequately controlled with diet and exercise. Cost Eff Resour Alloc 2020;18:12.
153. Yoshida Y, Cheng X, Shao H, et al. A systematic review of cost-effectiveness of sodium-glucose cotransporter inhibitors for type 2 diabetes. Curr Diab Rep 2020;20(4):12.
154. Ceriello A, Lucisano G, Prattichizzo F, et al. The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes. Lancet Reg Health Eur 2023;31:100666.